Run for your life: exercise, oxidative stress and the ageing endothelium

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Exercise is good for you. Elite athletes live longer than the general population (Teramoto & Bungum, 2009). Physically active middle-aged men live on average 2.3 years longer than sedentary men (Byberg *et al.* 2009). The mechanisms underlying the benefits of exercise on morbidity and mortality are multiple and complex (Williams *et al.* 2007; Heckman & McKelvie, 2008). The benefits of exercise training on blood pressure are well described and the mechanism for this may at least in part be due to improvements in endothelium-dependent vasodilatation (Heffernan *et al.* 2009). This is thought to result from increased shear stress in the arterial wall resulting in upregulation of genes coding for nitric oxide bioavailability (Kojda & Hambrecht, 2005). However, there are studies reporting no change in nitric oxide metabolism following exercise training in healthy humans (Green *et al.* 2004) and so the possibility exists that in some settings this mechanism is less important. In the elderly, forearm blood flow in response to acute exercise is impaired relative to younger subjects (Kirby *et al.* 2009); however, there is some evidence in older people that longer term exercise training can improve endothelium-dependent vasodilatation (Black *et al.* 2008).

In an article in a recent issue of *The Journal of Physiology*, Durrant *et al.* (2009) elegantly demonstrated that endothelial function, as assessed by acetylcholine induced relaxation, was restored in aged mice following 10–14 weeks of voluntary exercise on a running wheel to a level similar to that observed in younger mice that also have access to a wheel. The mechanism underlying this observation is suggested to be enhanced NO availability as a result of increased NOS expression, coupled with reduction in oxidative stress. Activity of the oxidant stress generating enzyme NADPH oxidase was reduced while activity of the free radical scavenging enzyme superoxide dismutase was increased in the aorta of free running aged mice. This study therefore demonstrates that the aged mouse endothelium retains an adaptive response to exercise that can re-establish vasodilatory function to that observed in younger mice. Furthermore, the mechanism for this appears to relate to reduced oxidative stress, which in turn permits greater bioavailability of nitric oxide.

While it is encouraging that endothelial function can be restored in ageing there are a number of key questions that arise from the underlying hypothesis implicit in this work and its relation to human ageing and disease.

Can elderly people exercise sufficiently to gain the potential benefits observed here?

The answer to this is likely to be no. While exercise training programmes do usually result in a range of health benefits, there is evidence that once intensive support and supervision is withdrawn, people simply return to their former sedentary behaviour (Dale *et al.* 2009). Mice, indeed all small rodents, on the other hand have a predilection for running and they will increase their running performance if rewarded with food (Klaus *et al.* 2009). Similar evidence for incentives to exercise in elderly people is lacking and indeed there is evidence that motivation for exercise diminishes significantly with age (O'Connor *et al.* 2004) due to complex social, cultural and gender reasons (Prohaska *et al.* 2006). Furthermore, the ageing population is increasingly living with significant degenerative co-morbidities, such as osteoarthritis, which limit the usefulness of exercise as an intervention to improve health on a population basis.

Is oxidative stress a key mechanism and can it be manipulated to contribute to the benefits of exercise in the human?

Antioxidants, such as vitamins C and E, appear to have benefits on endothelial function in the short term (Plantinga *et al.* 2007), but longer term studies have been negative (Kinlay *et al.* 2004). Indeed, a recent study suggested that acute ingestion of vitamin C or E after a programme of exercise training in the elderly paradoxically negated the benefits of training on blood pressure and forearm flow-mediated dilatation (Wray *et al.* 2009). Larger clinical trials of antioxidants as therapies to improve cardiovascular outcomes in both the primary and secondary prevention settings have now been largely abandoned after a series of negative studies (Bjelakovic *et al.* 2008).

In conclusion, the benefits of exercise are clear but you still need to take part. There appears to be no easy short-cut to these benefits. Eating more fresh fruit and vegetables is probably the best compromise. This should allow you to lower your cholesterol, enhance your antioxidant status and keep your weight down. This in turn is likely to allow you to avoid the illnesses, such as arthritis, that limit your ability to take part in regular exercise. After that, your endothelium is on its own!

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